EXHIBIT B TO PETITION

Docket No. 1177-001 Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
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FRANK D. MARCUM	:	
	:	GAU 1614
Serial No.: 10/686,918	:	
	:	Examiner Unknown
Filed: October 16, 2003	:	
	:	

For: COMPOSITION AND METHOD FOR TREATMENT AND PREVENTION OF TRAUMATIC SYNOVITIS AND DAMAGE TO ARTICULAR CARTILAGE

INFORMATION DISCLOSURE STATEMENT

Attn: Examiner Everett White
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

Applicant hereby discloses to the Examiner under 37 CFR § 1.56 and §1.97-1.98 as revised (1135 OG 13) and effective March 16, 1992, the information listed on the attached Form PTO/SB/08A. Review and consideration of this information during substantive examination of this application is respectfully requested.

In accordance with 37 CFR 1.97(h), the filing of this Information Disclosure Statement is not an admission that the information cited herein is, or is considered to be, material to patentability as defined in 37 CFR 1.56(d). Also, nothing in this statement is to be construed as a representation that this is the only information to be found, or the best. It,

however, is the only additional information known to the Applicantat this time and is believed to meet the requirements of 37 C.F.R. § 1.56. If additional qualifying references or other information is discovered in the future, such will be submitted promptly to fulfill Applicant's continuing duty of disclosure under 37 C.F.R. § 1.99.

Pursuant to M.P.E.P. § 708.02 VIII (E), a detailed discussion of the references is provided herein which points out how the claimed subject matter is patentable over the references. A copy of each reference, together with a listing on form PTO/SB/08A is submitted herewith. Applicant respectfully solicits the Examiner's consideration of the cited references and entry thereof into the record of this application.

Discussion of References Pursuant to M.P.E.P. § 708.02 VIII (E)

Reference A (US-2001/0046971 A1 to Hammerly)

Reference A, a US patent application publication (US-2001/0046971 A1) to Hammerly, was cited by Examiner White in the International Search Report issued from the ISA/US and mailed on August 6, 2004, for Applicant's corresponding PCT Application No. PCT/US03/32555 (International Publication Number WO 2004/034980 A3). The International Search Report conducted by Examiner White is believed to satisfy the requirements of M.P.E.P. § 708.02 VIII (C) and the following detailed discussion of the reference is provided pursuant to M.P.E.P. § 708.02 VIII (E).

Hammerly (Reference A) discloses a *required* combination of a "naturally-occurring"

chondroprotective agent and an analgesic for treatment of osteoarthritis. For Example, the "Technical Field" of the invention, paragraph 0002, states: "This invention relates to medicinal compositions of matter comprising an analgesic *in combination* with a naturally-occurring chondro-protective agent." (Emphasis added)

Moreover, according to: the title of the invention, "ANALGESICS *COMBINED* WITH NATURALLY-OCCURRING CHONDROPROTECTIVE AGENTS" (Emphasis added); the description of the preferred embodiments of the invention (*see, e.g.*, paragraph 0016); all eighteen (18) "Examples" which show the combination of an analgesic and a single chondro-protective agent; and the claims (*see, e.g.*, claim 1), Hammerly consistently teaches that the analgesic and chondro-protective agent are required to be in combination to achieve a superior therapeutic result. There is absolutely no teaching or suggestion that the "chondro-protective" agents disclosed by Hammerly, let alone the specific combination of Applicant's claimed invention, should be utilized without combination with the analgesic.

In fact, Hammerly actually teaches away from Applicants claimed invention. The point of novelty in Hammerly is set forth in paragraph 0010 wherein the reference states that no prior investigators have disclosed "an analgesic for short term relief of the symptoms of osteoarthritis in combination with a naturally-occurring chondroprotective agent that functions over the long term, and which thus work synergistically to simultaneously treat both the causality and the symptoms of OA." One motivated by the teachings of Hammerly would not be led to Applicant's claimed invention which utilizes a specific combination of

glucosamionglycans, namely hyaluronic acid and chondroitin sulfate and a metabolic precursor, namely N-Acetyl-D glucosamine, for the treatment and/or prevention of inflammatory arthritis, osteoarthritis and/or degenerative joint disease without the need of an analgesic in combination.

Hammerly in the "Background" in paragraph 0008 states that prior art disclosures of various naturally-occurring chondro-protective agents (NOCPA's) are capable of offering relief of symptoms in about 4-6 weeks but that "they offer no short term or immediate relief of OA symptoms." Thus, one motivated by the teachings of Hammerly would be led away from Applicant's claimed invention which, as set forth in the specification, does provide immediate relief of the symptoms of OA, in particular post surgically and in in the treatment and/or prevention of traumatic synovitis. (*See, e.g.*, paragraph 0002 "Field of the Invention" which teaches that the compositions of Applicant's claimed invention are useful for the treatment and prevention of inflammation of the synovial membrane and inflammatory arthritis. Likewise, paragraphs 0030, 0034, 0036 and 0042 describe the direct and immediate anti-inflammatory effect of Applicant's claimed compositions.) For example, the short term anti-inflammatory action of hyaluronic acid is disclosed in paragraph 0034, namely the direct removal of waste products from the joint capsule and inhibition of inflammatory mediators. Likewise, the short term anti-inflammatory action of chondroitin sulfate by direct inhibition of degenerative enzymes (paragraphs 0036 & 0037)is disclosed. These direct and short term benefits against the causal agents of inflammation and its

symptoms, according to Hammerly, are not present unless NOCPA's are combined with an analgesic. (*See*, paragraph 008, "they [the NOCPA's] offer no short term relief of OA symptoms"; *see also*, paragraph 0010.)

Moreover, the unique combination of Applicant's claimed compositions ,which are specifically formulated for intra-articular and other parenteral administration, provide a surprising synergistic effect for both the treatment and prevention of traumatic synovitis and damage to articular cartilage not heretofore taught or suggested by Hammerly or any of the prior art references known by applicant and disclosed herein. Thus, for the reasons set forth herein, it is submitted that Applicant's claimed invention is in no way obvious and/or anticipated by Reference A (Hammerly) either taken alone or in combination with the other references disclosed herein.

The above-referenced International Search Report conducted by Examiner White is believed to satisfy the requirements of M.P.E.P. § 708.02 VIII (C). In addition however and pursuant to the duty of disclosure under 37 C.F.R. § 1.56, Applicant discloses the following additional references listed on Form PTO/SB/08A.

Reference B (US-3,697,652 to Rovati et al.)

Reference B, US Patent No. 3,697,652 to Rovati et al. (cited in the background of Applicant's specification) entitled "N-ACETYLGLUCOSAMINE FOR TREATING DEGENERATIVE AFFLICTIONS OF THE JOINTS", discloses an injectable aqueous solution of N-Acetyl glucosamine for intramuscular or intraarticular injection. However,

in Rovati et al., there is absolutely no teaching or suggestion of Applicant's claimed compositions and methods. In fact, as with the Hammerly reference cited above, Rovati et al. states that "when the pharmaceutical preparations according to the invention are administered as injectable solutions, they should also contain a pain killing agent such as diethylamino-dimethylacetanilide hydrochloride." (*See,* column 2, lines 33-36, and Examples 2, 5 and 6). Thus, Applicant's claimed invention cannot be considered obvious in view of Rovati et al. either taken alone or in combination with the other art of record as set forth herein.

Reference C (US-4,801,619 to Lindblad)

Reference C, US Patent No. 4,801,619 (cited in the background of the Hammerly reference that was cited by Examiner White, Reference A above) to Lindblad for "HYALURONIC ACID PREPARATION TO BE USED FOR TREATING INFLAMMATIONS OF SKELETAL JOINTS", discloses the use of hyaluronic acid (HA) (and in particular a high molecular weight HA greater than 3×10^6 daltons for intra-articular treatment of inflammation and steroid arthropathy in joints. There is simply no teaching or suggestion in Lindblad of Applicant's claimed invention.

Reference D (US 4,808,576 to Schultz et al.)

Reference D, US Patent No. 4,808,576 to Schultz et al. entitled "REMOTE ADMINISTRATION OF HYALURONIC ACID TO MAMMALS", discloses the use of hyaluronic acid (HA) by parenteral administration other than intra-articular, using routes

such as intravenous, intramuscular, subcutaneous and topical. (*See, e.g.*, The Abstract) Again, in Schultz et al.,there is no teaching or suggestion of Applicant's claimed invention.

Reference E (US 5,364,845 to Henderson) &
Reference F (US 5,587,363 to Henderson)

Reference E, US Patent Nos.5,364,845 to Henderson (cited in the background of Applicant's specification) entitled "GLUCOSAMINE, CHONDROITIN AND MANGANESE COMPOSITION FOR THE PROTECTION AND REPAIR OF CONNECTIVE TISSUE", discloses an *oral* "neutraceutical" composition comprised of "therapeutic quantities of glucosamine and salts thereof, in combination with chondroitin sulfate and soluble salts of manganese, for stimulating production of proteoglycans and collagens in mammals in need thereof for treatment and repairing the connective tissue." (*See, e.g.,* claim 1, column 10). A continuation-in-part of the '845 patent to Henderson, US Patent No. 5,587,363 (Reference F, which was cited in the background of Applicant's specification) entitled "AMINOSUGAR AND GLYCOSAMINOGLYCAN COMPOSITION FOR THE TREATMENT AND REPAIR OF CONNECTIVE TISSUE" likewise discloses "neutraceutical" compositions comprised of "an aminosugar selected from the group consisting of glucosamine, glucosamine salts and mixtures thereof in combination with a glycosaminoglycan selected from the group consisting of chondroitin, chondroitin salts, and mixtures thereof." (*See, e.g.,* claim 1, column 11)

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In the '845 and '363 Henderson patents the compositions are formulated for oral use as a capsule for human and small animal oral administration and as an oral powder for large animals such as horses. (*See, e.g.*, column 7, lines 65-67 and column 8, lines 22-23 of the '363 patent). Both the '845 patent and the '363 patent to Henderson state that it is preferable to administer glucosamine orally: "glucosamine is almost completely absorbed when given orally (greater than 95%), as shown by animal and human studies. Even more important, 30% of an oral dose is retained by the musculoskeletal system for long time periods. *Daily oral dosing was found to raise tissue levels of glucosamine better than intravenous administration.* (*See, e.g.,* the '363 patent at column 7, lines 37-42). The '363 patent, states that the composition may be administered parenterally if desired (*See,* column 8, lines 42-43).

There is, however, no teaching or suggestion in the Henderson patents of the compositions or methods of Applicant's claimed invention which utilize compositions according to the invention that are specially adapted for parenteral administration and which comprise therapeutic amounts of a unique combination of: chondroitin sulfate; N-acetyl D-glucosamine; and hyaluronan (hyaluronic acid). Likewise, there is certainly no teaching or suggestion in the Henderson references, or in any of the references disclosed herein, of the surprising synergistic effect for both the treatment and prevention of traumatic synovitis and damage to articular cartilage that is provided by the unique combination of Applicant's claimed compositions, which are specifically formulated for intra-articular and other

parenteral administration. Thus, the claimed invention cannot be obvious in view of the Henderson references alone or in combination with the other art disclosed herein.

Reference G (Dorna & Guerrero, "Effects of Oral and Intramuscular Use of Chondroitin Sulfate in Induced Equine Aseptic Arthritis"; *Journal of Equine Veterinary Science*, September 1998)

Reference G, (the Dorna article) discloses a study that utilizes an experimental model of lameness created by injection of Freuds Complete Adjuvant into the knee of horses to create an aseptic arthritis for testing the efficacy of oral and intramuscular administrations of chondroitin sulfate (CS). In the study, 15 horses were divided into three groups as set forth in the "Methods and Materials" such that there were 5 control animals, 5 animals were treated post injury with oral chondroitin sulfate and 5 animals were treated post injury with intramuscular chondroitin sulfate. The animals were evaluated for a period of 30 days for certain parameters to access response to therapy. Following the evaluation period, in the "Conclusion", paragraph 3, Dorna states that: "[O]ur results here are evidence of the therapeutic value of CS in this intended pathology, irrespective of the route of administration."

Dorna (in the "Discussion", paragraphs 2-3) notes that there may be a direct anti-inflammatory effect of chondroitin sulfate with intramuscular injection based upon the early improvement in articular circumference measurement in the treated horses as is seen with the use of other glycosaminoglycans. In paragraph 3 of the "Discussion" Dorna further

notes that the early improvement (within 48 hours) of some of the evaluated parameters of the intramuscular treated group is consistent with greater bioavailibility of the product by this route of administration.

At paragraph 7 of the "Discussion", however, Dorna notes that the last 15 days of the study, there was no significant difference between treatment groups (oral and intramuscular) for all the parameters taken into account. And, finally, Dorna concludes the Discussion in paragraph 8 by noting the adverse effects of repeated parenteral administrations, suggesting that "parenteral applications (particularly intra-articular injections)" may not be an acceptable route of administration "when considering possible prophylactic schemes, especially in young animals in training."

Thus, Dorna does disclose that CS can be used successfully both parenterally and orally in the treatment of arthritis. However, it is suggested that the parenteral route is not preferred for prophylactic use due to the potential for adverse side effects. Moreover, there is no teaching or suggestion in Dorna to combine CS with other specific agents as set forth in Applicant's claimed invention, especially in a composition adapted for intra-articular or other parenteral administration comprised of therapeutic amounts of: chondroitin sulfate; N-acetyl D-glucosamine; and hyaluronan (hyaluronic acid). There is certainly no teaching in Dorna, or in any of the references disclosed herein, of the surprising synergistic effect for both the treatment and prevention of traumatic synovitis and damage to articular cartilage that is provided by the unique combination of Applicant's claimed compositions, which are

specifically formulated for intra-articular and other parenteral administration.

Summary

Thus, for the reasons set forth above Applicant respectfully contends that the claimed invention (as amended in the Preliminary Amendment being submitted concurrently herewith as Exhibit C to the Petition) is not obvious in view of the above-disclosed references either taken alone or in combination. In fact, as set forth above, certain of the references actually tend to teach away from Applicant's claimed invention. In particular, Henderson teaches that oral administration of glucosamine is better than intravenous administration; Hammerly and Rovati et al. teach that a pain killing agent should be administered in combination with a chondro-protective agent; and Dorna suggests that repeated parenteral (particularly intra-articular) administration of CS may cause adverse reactions. Certainly none of the references teaches or suggests the unique compositions and methods of the claimed invention and the surprising synergistic effect seen the for both the treatment and prevention of traumatic synovitis and damage to articular cartilage that is provided by the unique combination of Applicant's claimed compositions.

Therefore, the application is believed to be in condition for expedited review and

allowance thereof and such is earnestly solicited.

Respectfully submitted,

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November 2, 2004

Date

By J. W. Seanor, DVM

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Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet	1	of	1

Complete if Known	
Application Number	10/686,918
Filing Date	October 16, 2003
First Named Inventor	Marcum, Frank D.
Art Unit	1623
Examiner Name	Everett White
Attorney Docket Number	1177-001

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number - Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A	US-2001/0046971 A1	11-29-2001	Hammerly	
	B	US-3,697,652	10-10-1972	Rovati et al.	
	C	US-4,801,619	01-31-1989	Lindblad	
	D	US-4,808,576	02-28-1989	Schultz et al.	
	E	US-5,364,845	11-15-94	Henderson	
	F	US-5,587,563	12-24-1996	Henderson	
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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] - Number[4] - Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.
[1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	10/686,918
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First Named Inventor	Marcum, Frank D.
Group Art Unit	1623
Examiner Name	Everett White
Attorney Docket Number	1177-001

OTHER PRIOR ART -- NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	G	VIDELA DORNA I. DVM and C. GUERRERO DVM, Effects of Oral and Intramuscular use of Chondroitin Sulfate in Induced Equine Aseptic Arthritis, Journal of Equine Veterinary Science, September 1998	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.